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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/824,468	04/02/2001	Arthur M. Krieg	C1039/7049(HCL/MAT)	9046

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EXAMINER	
BLANCHARD, DAVID J	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 02/24/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/824,468	KRIEG ET AL.	
	Examiner	Art Unit	
	David J Blanchard	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 22-43 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 22-43 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 12/2/2003 has been entered.

2. Claims 22, 32, 36 and 38 have been amended in the Paper filed 10/6/2003.

3. Claims 22-43 are pending and under examination.

Specification

4. The disclosure is objected to because of the following informalities:

a. The disclosure contains USSNs that have issued as U.S. Patents. Applicant is requested to update the USSNs with their respective U.S. patent numbers. For example, see page 16, line 13 and pages 33-35. USSN 08/960,774 is now U.S. Patent 6,239,116 and USSN 08/738,652 is now U.S. Patent 6,207,646.

Appropriate correction is required.

Rejections Withdrawn

5. The rejection of claims 22-43 under 35 USC § 112, first paragraph, enablement, because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. This rejection is withdrawn in view of the declaration of Dr. Arthur Krieg filed 10/6/2003.

New Grounds of Rejection

Claim Rejections - 35 USC § 112

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

7. Claims 22-24, 26-30 and 32-34 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claims 22-24 and 26-30 are indefinite for reciting "antigen optionally additionally administered" in claim 22 and "antigen-cytokine fusion protein" in dependent claim 23. It is unclear if the "antigen optionally additionally administered" recited in claim 22 is the same or different than the antigen of the "antigen-cytokine fusion protein" recited in dependent claim 23. Does the "antigen-cytokine fusion protein" comprise the same antigen that is "optionally

additionally administered" in parent claim 22 or is some other antigen contemplated by the phrase "antigen-cytokine fusion protein"?

b. Claims 32-34 are indefinite for reciting "activating a dendritic cell of an immunostimulatory CpG" in claim 32. Specifically, the recitation "of an" renders the claim indefinite because the dendritic cell-immunostimulatory CpG relationship is unclear. Does the dendritic cell contain the CpG or is the dendritic cell activated with an immunostimulatory CpG oligonucleotide or is some other meaning contemplated by the phrase "activating a dendritic cell of an immunostimulatory CpG"?

Claim Rejections - 35 USC § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

9. Claim 32 is rejected under 35 U.S.C. 102(a) as being anticipated by Chace et al (Clinical Immunology and Immunopathology, 84(2):185-193, August 1997) as evidenced by Krieg A. M. (Trends in Microbiology, 4(2):73-77, February 1996).

Claim 32 recites a composition comprising an immunostimulatory CpG oligonucleotide at least 8 nucleotides in length and Il-3 or IL-12 wherein the C is unmethylated and the cytokine is a peptide. For this rejection, the intended use for "synergistically activating a dendritic cell", is given no patentable weight.

Chace et al teach co-administration of IL-12 and bacterial DNA, which comprises CpG dinucleotides that are unmethylated as evidenced by Krieg A. M (See pages 189-190 and Figure 9). Krieg A. M. teach CpG dinucleotides are present in bacterial DNA and bacterial DNA is unmethylated (see page 73).

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

11. Claims 22-32, 34-43 are rejected under 35 U.S.C. 103(a) as being obvious over Chace et al (Clinical Immunology and Immunopathology, 84(2):185-193, August 1997) as evidenced by Krieg A. M. [A] (Trends in Microbiology, 4(2):73-77, February 1996) in view of Krieg et al [B] (U.S. Patent 6,207,646 B1, 2/7/1995) and Maecker et al (Vaccine, 15(15):1687-1696, 10/7/1997).

Claims 22-31 recite a method for stimulating an immune response with an immunopotentiating cytokine selected from IL-3 or IL-12, and an immunostimulatory CpG oligonucleotide, wherein the CpG oligonucleotide is at least 8 nucleotides and C is unmethylated and the cytokine is a peptide administered as an antigen-cytokine fusion protein or in conjunction with the CpG olionucleotide and an antigen optionally administered, wherein the antigen is a tumor antigen, a microbial antigen, or an allergen and the subject is a non-human animal. The non-human animal subject is selected from the group consisting of a dog, a cat, a horse, a cow, a pig, a sheep, a goat, a chicken and a primate.

Claims 32, 34 and 35 are drawn to a composition comprising an immunopotentiating cytokine selected from IL-3 or IL-12, and an immunostimulatory CpG oligonucleotide, wherein the CpG oligonucleotide is at least 8 nucleotides and C is unmethylated and the cytokine is a peptide and the composition further comprises an antigen, wherein the antigen is selected from the group consisting of a cancer antigen, a microbial antigen, and an allergen. For this rejection, the intended use for "synergistically activating a dendritic cell", is given no patentable weight.

Claims 36-37 are drawn to a method for activating a dendritic cell, comprising contacting a dendritic cell exposed to a tumor antigen with an immunopotentiating cytokine selected from IL-3 or IL-12, and an immunostimulatory CpG oligonucleotide, wherein the CpG oligonucleotide is at least 8 nucleotides and C is unmethylated and the cytokine is a peptide and a tumor antigen may also be administered.

Claims 38-43 recite a method of treating a non-human animal subject having a neoplastic disorder by administering to the tumor an immunopotentiating cytokine selected from IL-3 or IL-12 and an immunostimulatory CpG oligonucleotide, wherein the CpG oligonucleotide is at least 8 nucleotides and C is unmethylated and the cytokine is a peptide. The non-human animal subject is selected from the group consisting of a dog, a cat, a horse, a cow, a pig, a sheep, a goat, a chicken and a primate and the tumor is selected from the group consisting of lymphoma and a tumor of the brain, lung, ovary, breast, prostate, colon and skin.

Chace et al teach co-administration of IL-12 and bacterial DNA, which comprises CpG dinucleotides that are unmethylated as evidenced by Krieg A. M (see page 189). Krieg A. M. [A] teach CpG dinucleotides are present in bacterial DNA and bacterial DNA is unmethylated (see page 73). Chace et al teach that NK cells alone did not produce IFN-gamma in response to bacterial DNA and NK cell stimulation with bacterial DNA in the presence of IL-12 promotes an IFN-gamma response that exceeds the maximum response seen with IL-12 stimulation alone (see pages 189-190 and Figure 9). Chace et al do not specifically teach a composition or a method of activating a dendritic cell, or a method for treating a subject having a neoplastic disorder with IL-3 or IL-12, and a CpG oligonucleotide wherein the CpG oligonucleotide is at least 8 nucleotides and C is unmethylated and the cytokine is a peptide and an antigen is optionally administered, wherein the antigen is a tumor antigen, a microbial antigen, or an allergen or an antigen-cytokine fusion protein in the method of stimulating an immune response. These deficiencies are made up for in the teachings of Krieg et al and Maecker et al.

Krieg et al [B] teach immunostimulatory nucleic acid molecules comprising the formula 5' X_1CGX_2 3' that are at least 8 nucleotides in length and can be used to treat, prevent or ameliorate a tumor or cancer, a viral, a fungal, a bacterial or parasitic infection in an individual and can be administered in conjunction with a vaccine, which is minimally comprised of an antigen (see columns 6 and 33). Krieg et al [B] teach that the immunpstimulatory CpG oligonucleotides may be administered in conjunction with an allergen to a subject

to treat or prevent an allergy (see column 6, lines 62-65, and column 34, lines 16-26). Krieg et al [B] teach that unmethylated CpG containing nucleic acid molecules preferentially activate monocytic cells such as dendritic cells as well as NK cells (see column 13, lines 11-15) and induced spleen cells to secrete numerous cytokines including IL-3 and IL-12 (see column 33, lines 22-26). Krieg et al teach subjects that are non-human animals including a dog, cat, horse, cow, pig, sheep, goat, chicken, monkey, rat, mouse, ect. (see column 13, lines 27-29). Krieg et al [B] also teach "conventional adjuvants only work for certain antigens, only induce an antibody (humoral) immune response (Th2), and are very poor at inducing cellular immune responses (Th1). For many pathogens, the humoral response contributes little to protection, and can even be detrimental" (see column 33, lines 56-61). Further, Krieg et al [B] teach that unmethylated CpG nucleic acids induce Th1 type cytokines (IL-12 and IFN-gamma) and shift the immune response in a subject from a Th2 to a Th1 response.

Maecker et al teach that immune responses to a model antigen (ovalbumin) can be enhanced by fusion to IL-12 and the ovalbumin-IL-12 fusion protein biased the immune response towards a Th1 profile (see page 1694, left column).

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced a composition and a method for activating a dendritic cell, a method for stimulating an immune response and a method for treating a subject having a neoplastic disorder with IL-12 and a CpG oligonucleotide, wherein the CpG oligonucleotide is at least 8

nucleotides and C is unmethylated and the cytokine is a peptide and an antigen is optionally administered, wherein the antigen is a tumor antigen, a microbial antigen, or an allergen and the cytokine may be administered as an antigen-cytokine fusion protein for therapeutic benefit.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have produced a composition and a method for activating a dendritic cell, a method for stimulating an immune response and a method for treating a subject having a neoplastic disorder with IL-12 and a CpG oligonucleotide, wherein the CpG oligonucleotide is at least 8 nucleotides and C is unmethylated and the cytokine is a peptide and an antigen is optionally administered, wherein the antigen is a tumor antigen, a microbial antigen, or an allergen and the cytokine may be administered as an antigen-cytokine fusion protein for therapeutic benefit in view of Chace et al and Krieg et al [B] and Maecker et al because Chace et al teach that co-administration of IL-12 and bacterial DNA and NK cells alone did not produce IFN-gamma in response to bacterial DNA, which comprises CpG dinucleotides that are unmethylated as evidenced by Krieg A. M [A] and Chace et al teach NK cell stimulation with bacterial DNA in the presence of IL-12 promotes an IFN-gamma response that exceeds the maximum response seen with IL-12 stimulation alone. In addition, one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have produced a composition and a method for activating a dendritic cell, a method for stimulating an immune response and a method for treating a subject having a neoplastic disorder with

IL-12 and a CpG oligonucleotide, wherein the CpG oligonucleotide is at least 8 nucleotides and C is unmethylated and the cytokine is a peptide and an antigen is optionally administered, wherein the antigen is a tumor antigen, a microbial antigen, or an allergen and the cytokine may be administered as an antigen-cytokine fusion protein for therapeutic benefit in view of Chace et al and Krieg et al and Maecker et al because Krieg et al [B] teach immunostimulatory nucleic acid molecules comprising the formula 5' X_1CGX_2 3' that are at least 8 nucleotides in length and can be used to treat, prevent or ameliorate a tumor or cancer, a viral, a fungal, a bacterial or parasitic infection in an individual and can be administered in conjunction with a vaccine, which is minimally comprised of an antigen or can be administered in conjunction with an allergen and unmethylated CpG nucleic acids preferentially activate dendritic cells and Krieg et al also teach "conventional adjuvants only work for certain antigens, only induce an antibody (humoral) immune response (Th2), and are very poor at inducing cellular immune responses (Th1). For many pathogens, the humoral response contributes little to protection, and can even be detrimental" (see column 33, lines 56-61). Further, Krieg et al [B] teach that unmethylated CpG nucleic acids induce Th1 type cytokines (IL-12 and IFN-gamma) and shift the immune response in a subject from a Th2 to a Th1 response and Maecker et al teach that an antigen-IL-12 fusion protein biased the immune response towards a Th1 profile. Thus, it would have been obvious to one skilled in the art to have produced a composition and a method for activating a dendritic cell, a method for stimulating an immune response and a method for treating a subject having a

neoplastic disorder with IL-12 and a CpG oligonucleotide, wherein the CpG oligonucleotide is at least 8 nucleotides and C is unmethylated and the cytokine is a peptide and an antigen is optionally administered, wherein the antigen is a tumor antigen, a microbial antigen, or an allergen and the cytokine may be administered as an antigen-cytokine fusion protein for therapeutic benefit in view of Chace et al and Krieg et al [B] and Maecker et al.

12. Claims 22-32 and 34-43 are rejected under 35 U.S.C. 103(a) as being obvious over Krieg et al (U.S. Patent 6,207,646 B1, 2/7/1995) in view of Gately et al (Therapeutic Immunology, 1:187-196, 1994) and Ballas et al (The Journal of Immunology, 157:1840-1845, 1996) and Noll et al (Infection and Immunity, 64(8):2955-2961, August 1996) and Levy et al (U.S. Patent 6,099,846, 102(e) date 4/14/1995).

The claims have been described supra.

Krieg et al have been described supra. Krieg et al do not specifically teach a composition or a method of activating a dendritic cell, a method of stimulating an immune response, and a method for treating a subject having a neoplastic disorder with IL-3 or IL-12, and a CpG oligonucleotide wherein the CpG oligonucleotide is at least 8 nucleotides and C is unmethylated and the cytokine is a peptide and an antigen is optionally administered, wherein the antigen is a tumor antigen, a microbial antigen, or an allergen or the cytokine is an antigen-cytokine fusion protein in the method of stimulating an immune

response. These deficiencies are made up for in the teachings of Gately et al and Ballas et al and Noll et al and Levy et al.

Gately et al teach that IL-12 increases NK lytic activity, enhances specific cytotoxic T lymphocyte responses, and promotes a Th1 type cytokine response. Gately et al teach that IL-12 cures infectious diseases by promoting a protective Th1 type response while inhibiting the development of a deleterious Th2-type response and anti-IL-12 antiserum was found to exacerbate infection, suggesting that IL-12 plays a pivotal role in the mechanism by which resolution of infectious diseases is achieved (see pages 189 and 190). Gately et al also teach that intratumoural injections and systemic administration of IL-12 in a number of tumor models resulted in substantial growth inhibition and prolongation of survival and, in some instances, complete tumor regression (see page 190 and Figure 3a). Thus, IL-12 has pronounced antitumor activity against a number of tumors following administration by several routes and can, under certain conditions, result in regression of established tumors (see pages 189-190). Gately et al teach that IL-12 has been shown to be more efficacious than IL-2 in several murine tumor models, and toxicology studies suggest that it may have a substantially better therapeutic index. Further, the long serum half-life of IL-12 relative to other cytokines will allow more flexibility in dosing schedules (see page 194).

Ballas et al teach that induction of NK activity by CpG nucleic acids requires IL-12. Neutralizing antibodies against IL-12 reduced the ability of CpG nucleic acids to induce lytic activity (see page 1843, left column and Figure 4).

Ballas et al teach that NK cells appear to be incapable of responding to the CpG oligonucleotides directly, but the response to the CpG oligonucleotides is mediated by cytokines (IL-12, IFN-alpha, IFN-β, and THF-alpha) released from accessory cells and dendritic cells appear to be the cellular source of these cytokines (see page 1843, right column).

Noll et al teach that IL-12 is an efficient alternative adjuvant to immunostimulating complexes for induction of protective CD4 Th1-cell dependent immune responses against enteropathogenic pathogens. Noll et al teach that *Yersinia enterocolitica* heat-shock protein 60 (Y-HSP60) plus IL-12 induced a much stronger proliferative T cell responses upon stimulation with Y-HSP60 preparations, as compared to T cell responses from mice immunized with Y-HSP60 alone or IL-12 alone (see page 2958 and Table 2). Noll et al teach that IL-12 enhances Th1 responses in *Yersinia* infections and can render *Yersinia*-susceptible mice resistant to this pathogen (see page 2959, left column). Noll et al also teach that numerous studies suggested that IL-12 can be used as an adjuvant. Hence, IL-12 is an essential component of a vaccine against *Leishmania major*, *Listeria monocytogenes*, *Toxoplasma gondii*, and *Mycobacterium tuberculosis,* all of which are intracellular pathogens (see page 2959, left column).

Levy et al teach tumor associated antigen-cytokine fusion proteins, which elicit immune responses, which are protective with respect to tumor proliferation and prolong survival time (see column 1, lines 47-52 and column 3 and Figure 8).

Levy et al also teach that an IL-2-herpes simplex virus type I glycoprotein fusion protein was previously shown to induce high antibody responses and cell-mediated immunity to HSV-I (see column 1, lines 39-46).

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced a composition and a method for activating a dendritic cell, a method for stimulating an immune response and a method for treating a subject having a neoplastic disorder with IL-12 and a CpG oligonucleotide in order to promote protective Th1 over detrimental Th2 responses and provide a synergistic therapeutic benefit, wherein the CpG oligonucleotide is at least 8 nucleotides and C is unmethylated and the cytokine is a peptide and an antigen is optionally administered, wherein the antigen is a tumor antigen, a microbial antigen, or an allergen or the cytokine is an antigen-cytokine fusion protein in the method of stimulating an immune response.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have produced a composition and a method for activating a dendritic cell, a method for stimulating an immune response and a method for treating a subject having a neoplastic disorder with IL-12 and a CpG oligonucleotide in order to promote protective Th1 over detrimental Th2 responses and provide a synergistic therapeutic benefit, wherein the CpG oligonucleotide is at least 8 nucleotides and C is unmethylated and the cytokine is a peptide and an antigen is optionally administered, wherein the antigen is a tumor antigen, a microbial antigen, or an allergen or the cytokine is

an antigen-cytokine fusion protein in the method of stimulating an immune response in view of Krieg et al and Gately et al and Ballas et al and Noll et al and Levy et al because Krieg et al teach immunostimulatory nucleic acid molecules comprising the formula 5' X_1CGX_2 3' that are at least 8 nucleotides in length and can be used to treat, prevent or ameliorate a tumor or cancer, a viral, a fungal, a bacterial or parasitic infection in an individual and can be administered in conjunction with a vaccine, which is minimally comprised of an antigen or can be administered in conjunction with an allergen and unmethylated CpG nucleic acids preferentially activate dendritic cells and Krieg et al also teach "conventional adjuvants only work for certain antigens, only induce an antibody (humoral) immune response (Th2), and are very poor at inducing cellular immune responses (Th1). For many pathogens, the humoral response contributes little to protection, and can even be detrimental" (see column 33, lines 56-61). Further, Krieg et al teach that unmethylated CpG nucleic acids induce Th1 type cytokines (IL-12 and IFN-gamma) and shift the immune response in a subject from a Th2 to a Th1 response and Gately et al teach that IL-12 cures infectious diseases by promoting a protective Th1 type response while inhibiting the development of a deleterious Th2-type response and IL-12 has pronounced antitumor activity against a number of tumors following administration by several routes and can, under certain conditions, result in regression of established tumors. Additionally, Gately et al teach that IL-12 has been shown to be more efficacious than IL-2 in several murine tumor models, and toxicology studies suggest that it may have a substantially better therapeutic index and the long serum half-life of IL-12 relative

to other cytokines will allow more flexibility in dosing schedules. In addition, one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have produced a composition and a method for activating a dendritic cell, a method for stimulating an immune response and a method for treating a subject having a neoplastic disorder with IL-12 and a CpG oligonucleotide in order to promote protective Th1 over detrimental Th2 responses and provide a synergistic therapeutic benefit, wherein the CpG oligonucleotide is at least 8 nucleotides and C is unmethylated and the cytokine is a peptide and an antigen is optionally administered, wherein the antigen is a tumor antigen, a microbial antigen, or an allergen or the cytokine is an antigen-cytokine fusion protein in the method of stimulating an immune response in view of Krieg et al and Gately et al and Ballas et al and Noll et al and Levy et al because Ballas et al teach neutralizing antibodies against IL-12 reduced the ability of CpG nucleic acids to induce lytic activity and Noll et al teach that IL-12 is an efficient alternative adjuvant to immunostimulating complexes for induction of protective CD4 Th1-cell dependent immune responses against enteropathogenic pathogens and Y-HSP60 plus IL-12 induced a much stronger proliferative T cell responses upon stimulation with Y-HSP60 preparations, as compared to T cell responses from mice immunized with Y-HSP60 alone or IL-12 alone and Levy et al teach tumor associated antigen-cytokine fusion proteins, which elicit immune responses, which are protective with respect to tumor proliferation and prolong survival time. Thus, it would have been obvious to one skilled in the art to have produced a composition and a method for activating a

dendritic cell, a method for stimulating an immune response and a method for treating a subject having a neoplastic disorder with IL-12 and a CpG oligonucleotide in order to promote protective Th1 over detrimental Th2 responses and provide a synergistic therapeutic benefit, wherein the CpG oligonucleotide is at least 8 nucleotides and C is unmethylated and the cytokine is a peptide and an antigen is optionally administered, wherein the antigen is a tumor antigen, a microbial antigen, or an allergen or the cytokine is an antigen-cytokine fusion protein in the method of stimulating an immune response in view of Krieg et al and Gately et al and Ballas et al and Noll et al and Levy et al.

It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose in order to form a third composition that is to be used for the very same purpose, idea of combining them flows logically from their having been individually taught in the prior art. In re Kerkhoven, 205 USPQ 1069, CCPA 1980. See MPEP 2144.06.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

13. Claims 22-31 and 38-43 are rejected under 35 U.S.C. 103(a) as being obvious over Krieg et al (U.S. Patent 6,207,646 B1, 2/7/1995) in view of Noll et al (Infection and Immunity, 64(8):2955-2961, August 1996) and Brunda M. J. (Res. Immun., 146:622-628, Sept-Oct 1995) and Pulaski et al (Cancer Research,

53:2112-2117, 1993) and Korenaga et al (Parasitology Research, 82:108-113, 1996) and Levy et al (U.S. Patent 6,099,846, 102(e) date 4/14/1995).

The claims have been described supra.

Krieg et al have been described supra. Krieg et al do not specifically teach a method of stimulating an immune response, or a method for treating a subject having a neoplastic disorder with IL-3 or IL-12, and a CpG oligonucleotide wherein the CpG oligonucleotide is at least 8 nucleotides and C is unmethylated and the cytokine is a peptide and an antigen is optionally administered, wherein the antigen is a tumor antigen, a microbial antigen, or an allergen or the cytokine is an antigen-cytokine fusion protein in the method of stimulating an immune response. These deficiencies are made up for in the teachings of Noll et al and Brunda M. J. and Pulaski et al and Korenaga et al and Levy et al.

Noll et al have been described supra.

Brunda M. J. teach that local or systemic delivery of IL-12 resulted in marked anti-tumor efficacy in mice bearing a variety of malignancies and IL-12 was more effective than IL-2 in several tumor models (see page 623, left column). Brunda M. J. teach the use of IL-12 as an adjuvant for a tumor vaccine and treatment with the combination of tumor peptide and IL-12 resulted in tumor regression, while no anti-tumor effect was observed with tumor peptide or IL-12 alone (see page 623, right column). Brunda M. J. teach that combining IL-12 with other agents may enhance its utility and point out direction to pursue in clinical trials (see page 625, right column).

Pulaski et al teach that expression of IL-3 in line 1 tumor cells have a novel effect on the generation of antitumor cytotoxic effectors, and indeed stimulate CTL as well as IL-2, a known T-cell growth factor (see page 2115). Pulaski et al teach that the finding that IL-3 aids in the generation of anti-tumor CTL may ultimately be important when designing therapies or vaccines to specifically enhance particular subsets of effectors such as CTL (see page 2117).

Korenaga et al teach that administration of recombinant IL-3 (rIL-3) hastened worm expulsion in *Trichinella spiralis*-infetced mice (see abstract and Figure 1).

Levy et al have been described supra.

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced a method for stimulating an immune response and a method for treating a subject having a neoplastic disorder with IL-3 or IL-12, and a CpG oligonucleotide, wherein the CpG oligonucleotide is at least 8 nucleotides and C is unmethylated and the cytokine is a peptide and an antigen is optionally administered, wherein the antigen is a tumor antigen, or a microbial antigen and the cytokine may be an antigen-cytokine fusion protein in the method of stimulating an immune response.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have produced a method for stimulating an immune response and a method for treating a subject having a neoplastic disorder with IL-3 or IL-12, and a CpG oligonucleotide, wherein the CpG

oligonucleotide is at least 8 nucleotides and C is unmethylated and the cytokine is a peptide and an antigen is optionally administered, wherein the antigen is a tumor antigen, or a microbial antigen and the cytokine may be an antigen-cytokine fusion protein in the method of stimulating an immune response in view of Krieg et al and Noll et al and Brunda M. J. and Pulaski et al and Korenaga et al and Levy et al because Krieg et al teach immunostimulatory nucleic acid molecules comprising the formula 5' X_1CGX_2 3' that are at least 8 nucleotides in length and can be used to treat, prevent or ameliorate a tumor or cancer, a viral, a fungal, a bacterial or parasitic infection in an individual and can be administered in conjunction with a vaccine, which is minimally comprised of an antigen and Noll et al teach that IL-12 is an efficient alternative adjuvant to immunostimulating complexes for induction of protective CD4 Th1-cell dependent immune responses against enteropathogenic pathogens and Y-HSP60 plus IL-12 induced a much stronger proliferative T cell responses upon stimulation with Y-HSP60 preparations, as compared to T cell responses from mice immunized with Y-HSP60 alone or IL-12 alone and Brunda M. J. teach the use of IL-12 as an adjuvant for a tumor vaccine and treatment with the combination of a tumor peptide and IL-12 resulted in tumor regression, while no anti-tumor effect was observed with either the tumor peptide or IL-12 alone. In addition, one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have produced a method for stimulating an immune response and a method for treating a subject having a neoplastic disorder with IL-3 or IL-12, and a CpG oligonucleotide, wherein the CpG oligonucleotide is at

least 8 nucleotides and C is unmethylated and the cytokine is a peptide and an antigen is optionally administered, wherein the antigen is a tumor antigen, or a microbial antigen and the cytokine may be an antigen-cytokine fusion protein in the method of stimulating an immune response in view of Krieg et al and Noll et al and Brunda M. J. and Pulaski et al and Korenaga et al and Levy et al because Puklaski et al teach that IL-3 in tumor cells has a novel effect on the generation of antitumor cytotoxic effectors, and indeed stimulate CTL as well as IL-2, a known T-cell growth factor and Korenaga et al teach that administration of recombinant IL-3 (rIL-3) hastened worm expulsion in *Trichinella spiralis*-infetced mice and Levy et al. Thus, it would have been obvious to one skilled in the art to have produced to have produced a method for stimulating an immune response and a method for treating a subject having a neoplastic disorder with IL-3 or IL-12, and a CpG oligonucleotide, wherein the CpG oligonucleotide is at least 8 nucleotides and C is unmethylated and the cytokine is a peptide and an antigen is optionally administered, wherein the antigen is a tumor antigen, or a microbial antigen and the cytokine may be an antigen-cytokine fusion protein in the method of stimulating an immune response in view of Krieg et al and Noll et al and Brunda M. J. and Pulaski et al and Korenaga et al and Levy et al.

It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose in order to form a third composition that is to be used for the very same purpose, idea of combining them flows logically from their having been individually taught in the prior art. In re Kerkhoven, 205 USPQ 1069, CCPA 1980. See MPEP 2144.06.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

Double Patenting

14. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

15. Claims 22-43 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-2, 4-12 and 14-23 of U.S. Patent No. 6,218,371 B1 in view of Gately et al (Therapeutic Immunology, 1:187-196, 1994) and Ballas et al (The Journal of Immunology, 157:1840-1845, 1996) and Pulaski et al (Cancer Research, 53:2112-2117, 1993) and Korenaga et al (Parasitology Research, 82:108-113, 1996). Although the conflicting claims are not identical, they are not patentably distinct from each other.

The claims in the instant application are drawn to a composition and a method for activating a dendritic cell, a method for stimulating an immune response and a method for treating a subject having a neoplastic disorder with IL-3 or IL-12, and a CpG oligonucleotide, wherein the CpG oligonucleotide is at least 8 nucleotides and C is unmethylated and the cytokine is a peptide and an antigen is optionally administered, wherein the antigen is a tumor antigen, a microbial antigen, or an allergen and the cytokine may be administered as an antigen-cytokine fusion protein in the method of stimulating an immune response.

Claims 1-2, 4-12 and 14-23 of U.S. Patent 6,218,371 B1 are drawn to a composition and a method for activating a dendritic cell, a method for stimulating an immune response and a method for treating a subject having a neoplastic disorder with GM-CSF, or IL-2, or IL-4, or IFN-gamma, and a CpG oligonucleotide, wherein the CpG oligonucleotide is at least 8 nucleotides and C is unmethylated and the cytokine is a peptide and an antigen is optionally administered, wherein the antigen is a tumor antigen, a microbial antigen, or an allergen and the cytokine may be administered as an antigen-cytokine fusion protein in the method of stimulating an immune response. The claims in U.S. Patent 6,218,371 B1 do not specifically teach administration of Il-3 or IL-12, and a CpG oligonucleotide. These deficiencies are made up for in the teachings of Gately et al and Pulaski et al and Korenaga et al.

Gately et al teach that IL-12 increases NK lytic activity, enhances specific cytotoxic T lymphocyte responses, and promotes a Th1 type cytokine response. Gately et al teach that IL-12 cures infectious diseases by promoting a protective

Th1 type response while inhibiting the development of a deleterious Th2-type response and anti-IL-12 antiserum was found to exacerbate infection, suggesting that IL-12 plays a pivotal role in the mechanism by which resolution of infectious diseases is achieved (see pages 189 and 190). Gately et al also teach that intratumoural injections and systemic administration of IL-12 in a number of tumor models resulted in substantial growth inhibition and prolongation of survival and, in some instances, complete tumor regression (see page 190 and Figure 3a). Thus, IL-12 has pronounced antitumor activity against a number of tumors following administration by several routes and can, under certain conditions, result in regression of established tumors (see pages 189-190). Gately et al teach that IL-12 has been shown to be more efficacious than IL-2 in several murine tumor models, and toxicology studies suggest that it may have a substantially better therapeutic index. Further, the long serum half-life of IL-12 relative to other cytokines will allow more flexibility in dosing schedules (see page 194).

Ballas et al teach that induction of NK activity by CpG nucleic acids requires IL-12. Neutralizing antibodies against IL-12 reduced the ability of CpG nucleic acids to induce lytic activity (see page 1843, left column and Figure 4). Ballas et al teach that NK cells appear to be incapable of responding to the CpG oligonucleotides directly, but the response to the CpG oligonucleotides is mediated by cytokines (IL-12, IFN-alpha, IFN-β, and THF-alpha) released from accessory cells and dendritic cells appear to be the cellular source of these cytokines (see page 1843, right column)

Pulaski et al teach that expression of IL-3 in line 1 tumor cells have a novel effect on the generation of antitumor cytotoxic effectors, and indeed stimulate CTL as well as IL-2, a known T-cell growth factor (see page 2115). Pulaski et al teach that the finding that IL-3 aids in the generation of anti-tumor CTL may ultimately be important when designing therapies or vaccines to specifically enhance particular subsets of effectors such as CTL (see page 2117).

Korenaga et al teach that administration of recombinant IL-3 (rIL-3) hastened worm expulsion in *Trichinella spiralis*-infetced mice (see abstract and Figure 1)

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced a composition and a method for activating a dendritic cell, a method for stimulating an immune response and a method for treating a subject having a neoplastic disorder with IL-3 or IL-12, and a CpG oligonucleotide, wherein the CpG oligonucleotide is at least 8 nucleotides and C is unmethylated and the cytokine is a peptide and an antigen is optionally administered, wherein the antigen is a tumor antigen, a microbial antigen, or an allergen or the cytokine is an antigen-cytokine fusion protein in the method of stimulating an immune response in view of the teachings of Gately et al and Ballas et al and Pulaski et al and Korenaga et al.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have produced a composition and a method for activating a dendritic cell, a method for stimulating an immune

response and a method for treating a subject having a neoplastic disorder with IL-3 or IL-12, and a CpG oligonucleotide, wherein the CpG oligonucleotide is at least 8 nucleotides and C is unmethylated and the cytokine is a peptide and an antigen is optionally administered, wherein the antigen is a tumor antigen, a microbial antigen, or an allergen or the cytokine is an antigen-cytokine fusion protein in the method of stimulating an immune response in view of the teachings of Gately et al and Ballas et al and Pulaski et al and Korenaga et al because Gately et al teach that IL-12 cures infectious diseases and intratumoural injections and systemic administration of IL-12 in a number of tumor models resulted in substantial growth inhibition and prolongation of survival and, in some instances, complete tumor regression and Ballas et al teach that that induction of NK activity by CpG nucleic acids requires IL-12 and neutralizing antibodies against IL-12 reduced the ability of CpG nucleic acids to induce lytic activity (see page 1843, left column and Figure 4). Further, Ballas et al teach that NK cells appear to be incapable of responding to the CpG oligonucleotides directly, but the response to the CpG oligonucleotides is mediated by cytokines (IL-12, IFN-alpha, IFN-β, and THF-alpha) released from accessory cells and dendritic cells appear to be the cellular source of these cytokines. In addition, one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have produced a composition and a method for activating a dendritic cell, a method for stimulating an immune response and a method for treating a subject having a neoplastic disorder with IL-3 or IL-12, and a CpG oligonucleotide, wherein the CpG oligonucleotide is at least 8 nucleotides and C

is unmethylated and the cytokine is a peptide and an antigen is optionally administered, wherein the antigen is a tumor antigen, a microbial antigen, or an allergen or the cytokine is an antigen-cytokine fusion protein in the method of stimulating an immune response in view of the teachings of Gately et al and Ballas et al and Pulaski et al and Korenaga et al because Pulaski et al teach that IL-3 aids in the generation of anti-tumor CTL and may ultimately be important when designing therapies or vaccines to specifically enhance particular subsets of effectors such as CTL and Korenaga et al teach that administration of recombinant IL-3 (rIL-3) hastened worm expulsion in *Trichinella spiralis*-infetced mice. Thus, it would have been obvious to one skilled in the art to have produced a composition and a method for activating a dendritic cell, a method for stimulating an immune response and a method for treating a subject having a neoplastic disorder with IL-3 or IL-12, and a CpG oligonucleotide, wherein the CpG oligonucleotide is at least 8 nucleotides and C is unmethylated and the cytokine is a peptide and an antigen is optionally administered, wherein the antigen is a tumor antigen, a microbial antigen, or an allergen or the cytokine is an antigen-cytokine fusion protein in the method of stimulating an immune response in view of the teachings of Gately et al and Ballas et al and Pulaski et al and Korenaga et al.

Conclusion

16. No claim is allowed.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Blanchard whose telephone number is (571) 272-0827. The examiner can normally be reached at (571) 272-0827 from 8:00 AM to 5:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, can be reached at (571) 272-0871.

Official papers related to this application may be submitted to Group 1600 by facsimile transmission. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The official fax number for Group 1600 where this application or proceeding is assigned is (703) 872-9306.

Respectfully,
David J. Blanchard
571-272-0827